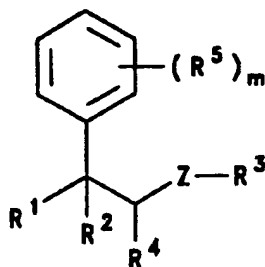


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(54) Title: PHENYL DERIVATIVES USEFUL AS TACHYKININ ANTAGONISTS

(I)

(57) Abstract

Compounds of formula (I), or a salt or prodrug thereof are tachykinin antagonists.

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PHENYL DERIVATIVES USEFUL AS TACHYKININ ANTAGONISTS

5 This invention relates to a class of aromatic compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention contain a phenyl moiety and hydroxyl or ether moiety.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout
10 mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The structures of three known mammalian tachykinins are as follows:

Substance P:

15 Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

20 For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba
25 Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009) and in arthritis
30 [Levine et al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh et al in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster

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Headache" Ed. Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al Science (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press], and in disorders of bladder function such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

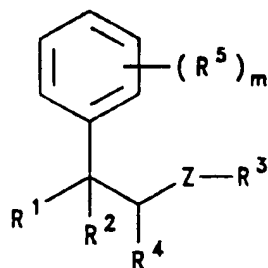
It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as

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poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), opthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989).

We have now found a class of non-peptides which are potent antagonists of tachykinin.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

R^1 represents a nitrogen containing aromatic or non-aromatic heterocycle optionally substituted by one or more groups selected from C_1 -6alkyl, C_1 -6alkoxy, oxo, thioxo, halo, trifluoromethyl, nitro, NR^aR^b , NR^aCOR^b , CONR^aR^b , CO_2R^a , SO_2R^a and CH_2OR^a , where R^a and R^b each independently represent H, C_1 -6alkyl or phenyl optionally substituted by C_1 -6alkyl, halo or trifluoromethyl;

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R^2 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

R^3 represents C_{1-3} alkyl substituted by a phenyl group which may itself optionally be substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C , SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ and $CONR^C R^d$;

R^4 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

each R^5 independently represents C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl;

Z represents O or S; and

m represents 0, 1, 2 or 3.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the formulae herein may represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

For phenylalkyl substituents, the alkyl moiety may be straight or branched.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo.

Aptly R^1 represents an optionally substituted aromatic heterocycle.

The nitrogen containing aromatic heterocycle represented by R^1 may be, for example, a 5- or 6-membered heterocycle and may contain, in addition to the nitrogen atom, one or more heteroatoms selected from O, S and N, or groups NR^8 , where R^8 is H or C_{1-6} alkyl.

Suitably R^1 represents an optionally substituted 5-membered heteroaryl moiety selected from pyrrolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl,

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oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl and imidazolyl. Preferably R^1 represents optionally substituted pyrrolyl or imidazolyl. More preferably R^1 represents imidazolyl substituted by a nitro or an amino group.

Aptly R^1 represents an optionally substituted non-aromatic heterocycle.

Suitably R^1 represents a 4, 5, 6, 7 or 8 membered ring which may have one heteroatom in addition to the nitrogen atom, for example an oxygen atom. Apt groups include those of the formula

wherein Q is CH_2 , NR^8 where R^8 is as hereinbefore defined, O or S, n^1 is 1, 2 or 3 and m^1 is 1 or 2 with the proviso that when Q is NR^8 , O or S neither n^1 nor m^1 is 1; which group can be optionally substituted by one or two oxo groups or C_{1-6} alkyl groups.

A favoured non-aromatic group R^1 is morpholino. R^1 is linked to carbon atom which also bears the R^2 group and the other groups shown in formula (I) via the nitrogen atom.

Suitable values for the groups R^2 and R^4 include H and methyl, preferably H.

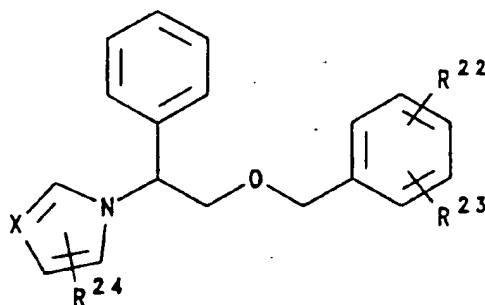
Suitably R^3 represents a C_{1-3} alkyl chain bearing a substituent which is a substituted phenyl group. Suitable phenyl substituents include methyl, methoxy, nitro, cyano, halo and trifluoromethyl. Preferably R^3 represents methyl substituted by a

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substituted phenyl group. Preferably one or two substituents will be present in the phenyl ring. More preferably R^3 represents methyl substituted by 3,5-disubstituted phenyl, such as 3,5-dimethylphenyl or 3,5-bistrifluoromethylphenyl.

Preferably m represents zero.

A preferred sub-class of compounds according to the invention is represented by formula (Ia):



(Ia)

wherein

X is N or CH;

R^{22} and R^{23} each independently represent H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, hydroxy, phenoxy or amino;

R^{24} is NO_2 or NH_2 , and may be located at any available ring position; and salts and prodrugs thereof.

Specific compounds within the scope of the present invention include:

(+)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(2,5-dimethylpyrrole)-2-phenylethane;
1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(imidazole)-2-phenylethane;
(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(2-nitroimidazole)-2-phenylethane;

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(±)-2-N(2-aminoimidazole)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-phenylethane;
(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(4-nitroimidazole)-2-phenylethane;
5 (±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]2-N-morpholino-2-phenylethane;
(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]2-N-(piperidine-2,6-clione-2-phenylethane
and salts and prodrugs thereof especially the
10 pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the
15 invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the
20 invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise
25 quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may
30 include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In

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general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and
5 preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The present invention includes within its scope solvates of the compounds of formula (I) and salts
10 thereof, for example, hydrates.

The compounds according to the invention have at least one asymmetric centre, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are
15 encompassed within the scope of the present invention.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier.

20 Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or
25 insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose,
30 sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-

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toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium

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carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such

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as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases, particularly those associated with excess mucus secretion such as

5 chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and

10 rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as

15 alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as

20 systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor

25 hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable

30 to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as,

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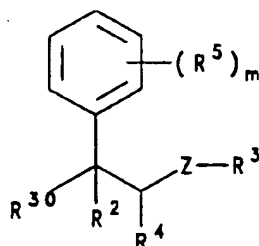
for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

5 The present invention further provides a compound of formula (I) for use in therapy. According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of
10 physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which
15 method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

 In the treatment of the conditions associated
20 with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain
25 sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

30 The compounds according to the invention may be prepared from compounds of formula (II)

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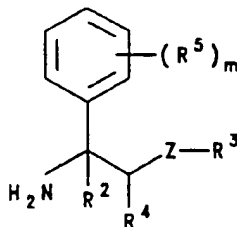
(II)

- 10 wherein R², R³, R⁴, R⁵, Z and m are as defined for
 formula (I) above and R³⁰ represents a leaving group, by
 reaction with a metallated aromatic heterocycle of formula
 R¹-M wherein R¹ is as defined for formula (I) and M
 represents a metal, such as an alkali metal, for example
 15 sodium or lithium, or with a non-aromatic amine R¹-H,
 optionally in the presence of a tertiary amine base.

Suitable leaving groups represented by R³⁰
 include aryl and alkyl sulphonate groups, such as
 tosylate and mesylate groups.

- 20 The reaction is conveniently effected in a
 suitable organic solvent, such as dimethyl formamide, or
 an ether, such as, for example, tetrahydrofuran, or a
 mixture thereof, suitably at room temperature.

- Alternatively, compounds of formula (I) may be
 25 prepared from compounds of formula (III)



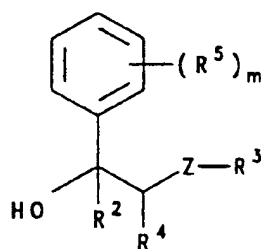
(III)

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wherein R^2 , R^3 , R^4 , R^5 , Z and m are defined for formula (I) using conventional methods for the construction of the heteroaromatic ring. Suitable methods are described, for example, in Comprehensive Heterocyclic Chemistry, 5 Katritzky and Rees, Pergamon Press, 1984.

Compounds of formula (I) may also be prepared from other compounds of formula (I) by interconversion processes. Such processes are particularly useful for modifying substituents in the heteroaromatic ring. For 10 example, compounds of formula (I) wherein R^1 represents a heteroaryl moiety substituted by an amino group may be prepared from the corresponding compounds of formula (I) wherein R^1 represents the same heteroaryl moiety substituted by a nitro group, by reduction. Further 15 suitable interconversion procedures will be readily apparent to those skilled in the art.

Compounds of formula (II) may be prepared from intermediates of formula (IV)



(IV)

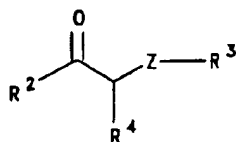
wherein R^2 , R^3 , R^4 , R^5 , Z and m are as defined for formula (I), by conversion of the hydroxy group to a leaving group under conventional conditions, for example, 30 by reaction with a compound of formula R^{30} -Hal, where Hal represents halo, such as chloro or bromo, in the presence of a base.

Suitable bases of use in the reaction include tertiary amines such as, for example, triethylamine.

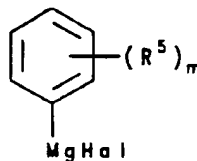
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The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, diethyl ether.

Intermediates of formula (IV) may be prepared
 5 by reaction of compounds of formula (V) with compounds of formula (VI)



(V)

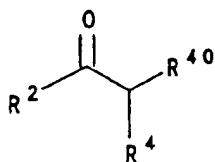


(VI)

15 wherein R^2 , R^3 , R^4 , R^5 , Z, m and Hal are as previously defined.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, diethyl ether.

20 Compounds of formula (V) may be prepared by reaction of a compound of formula (VII), or an appropriately protected derivative thereof, with a compound of formula (VIII)



(VII)



(VIII)

Wherein R^2 , R^3 and R^4 are as previously defined, one of R^{40} and R^{41} represents ZH where Z is as previously defined and the other of R^{40} and R^{41}

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represents a leaving group, in the presence of a base, followed by deprotection, if required.

Suitably R^{40} represents ZH and R^{41} represents a leaving group.

5 Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

10 The reaction is conveniently carried out in a suitable organic solvent, such as dimethylformamide, at a temperature in the region of 0°C. Favoured bases of use in the reaction include alkali metal hydrides, such as sodium hydride.

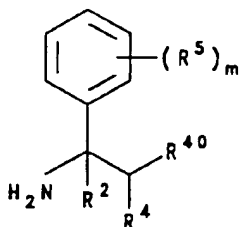
15 The intermediates of formula (VII) above wherein R^{40} is SH may be prepared from the corresponding intermediates of formula (VII) wherein R^{40} represents OH by treating the latter compound with hydrogen sulphide in the presence of aluminium oxide, as described by Lucien et al., Nouveau J. Chem., 3, 15 (1979), or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at
20 ambient or elevated temperatures, suitably at reflux temperature.

25 Intermediates of formula (VII) wherein R^{40} is a leaving group may be prepared from intermediates of formula (VII) wherein R^{40} represents OH as described for the preparation of compounds of formula (II) from
30 compounds of formula (IV) above.

30 Intermediates of formula (VII) wherein R^{40} is OH are commercially available or may be prepared from commercially available starting materials by conventional procedures which will be readily apparent to those skilled in the art.

 Intermediates of formula (III) may be prepared from compounds of formula (IX)

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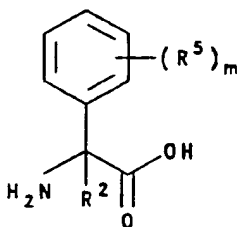


(IX)

wherein R^2 , R^4 , R^5 , R^{40} and m are as previously defined,
 10 by reaction with compounds of formula (VIII) as
 previously defined, in the presence of a base, as
 described for the preparation of compounds of formula (V)
 above.

Compounds of formula (IX) wherein R^{40} is SH or
 15 a leaving group may be prepared from compounds of formula
 (IX) wherein R^{40} is OH analogously to the preparation of
 compounds of formula (VII) wherein R^{40} is SH or a leaving
 group.

Compounds of formula (IX) wherein R^4 is H and
 20 R^{40} is OH may be prepared from compounds of formula (X)



(X)

wherein R^2 , R^5 and m are as previously defined, or alkyl
 30 esters thereof, by reduction.

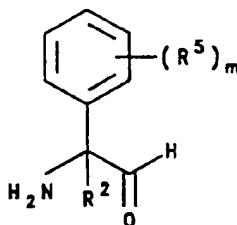
Suitable reducing agents include metal
 hydrides, such as lithium aluminium hydride. The
 reaction is conveniently effected in a suitable organic
 solvent, such as ether, for example, tetrahydrofuran,

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suitably at elevated temperature, such as the reflux temperature of the solvent.

Compounds of formula (X) are commercially available or may be prepared by conventional procedures for the preparation of amino acids which are well documented and are described, for example, in Chemistry and Biochemistry of the Amino Acids, ed. G. C. Barrett, Chapman and Hall, 1985.

Compounds of formula (IX) wherein R^{40} is OH and R^4 is other than H may be prepared from intermediates of formula (XI)



(XI)

wherein R^2 , R^5 and m are as defined for formula (I), by reaction with an organometallic reagent of formula MR^4 , wherein R^4 is as previously defined and M represents a metal, such as lithium, or a metal halide, such as a magnesium halide, e.g. magnesium chloride or magnesium bromide.

The reaction is suitably effected in an inert organic solvent such as an ether, for example, diethylether or tetrahydrofuran.

Aldehydes of formula (XI) may be prepared by reduction of esters of compounds of formula (X) using diisobutylaluminium hydride.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers

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may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, compounds of formula (I) wherein R^1 is H may be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. These compounds can then be used to make individual enantiomers of compounds of formula (I) wherein R^1 is other than H.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

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EXAMPLE 1

(+)-1-[(3,5-Bistrifluoromethylphenyl)methyloxy]-2-N(2,5-dimethyl pyrrole)-2-phenyl ethane

5 a) L-2-Phenylglycinol (5g) and di-t-butylidicarbonate (9.4g) was stirred in a dichloromethane solution (30ml) at room temperature for 3 hours. The precipitate which formed was filtered to give N-t-butoxycarbonyl-L-2-phenylglycinol, 4g.

10 b) To a solution of 2-N-t-butoxycarbonylamino-L-2-phenylglycinol (23.7g; Example 1a) and 3,5-bis(trifluoromethyl)benzyl bromide (33.8g) dissolved in dimethylformamide (75ml) was added sodium hydride (80% suspension in oil, 3.3g) in portions over 30 minutes. After stirring the solution at ambient temperature for 1h, water 15 (500ml) and ethyl acetate (500ml) were added. The organic phase was washed further with water (2 x 100ml), saturated brine and dried (MgSO₄). After evaporation *in vacuo* the residue was chromatographed on silica (eluting with 5% ethyl acetate in petroleum ether bp 60-80°C) to give 20 (S)-1-(3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-N-t-butoxycarbonylamino-2-phenylethane, m.p. 53-54°C.

25 c) The product of Example 1b (10g) was allowed to stand in 250ml of diethyl ether saturated with gaseous HCl. The solvent was removed *in vacuo* and the residue recrystallised from diethyl ether-petroleum ether to give crystalline (+)-2-ammonium-1-(bistrifluoromethylphenyl)methyloxy-2-phenyl ethane, hydrochloride salt.

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d) To a solution of (+)-2-ammonium-1-(bistrifluoromethylphenyl)methoxy-2-phenyl ethane, hydrochloride salt (1mmol) and 1.1 equivalents of 2,5-hexanedione in 5ml methanol was added potassium hydroxide (1.5mmol). The reaction was refluxed for 48h and partitioned between dichloromethane-water. The organic phase was separated, dried (MgSO_4), concentrated *in vacuo*, and poured through a plug of silica using 5% ethyl acetate-pet. ether as eluent. The filtrate was concentrated to give the title compound as a clear oil: (CDCl_3) δ 2.05 (6H, s), 4.1-4.15 (1H, m), 4.4-4.45 (1H, m), 4.5-4.7 (2H, m), 5.6-5.65 (1H, m), 5.8 (2H, s), 7.1-7.15 (2H, m), 7.2-7.4 (3H, m), 7.7 (2H, s), 7.8 (1H, s); Found: C, 62.43; H, 4.83; N, 3.32. $\text{C}_{23}\text{H}_{21}\text{NOF}_6$ requires: C, 62.58; H, 4.79; N, 3.17.

EXAMPLE 2

1-[(3,5-Bistrifluoromethylphenyl)methoxy]-2-N(imidazole)-2-phenyl ethane

a) To a stirred solution of solketal (0.151mol) in DMF/THF (1:1, 300ml) under a nitrogen atmosphere was added sodium hydride (1.2 equivalents of an 80% dispersion in mineral oil). The anion was allowed to form over one hour prior to addition of 3,5-bistrifluoromethylbenzyl bromide. The reaction was partitioned between ethyl acetate-saturated ammonium chloride after 1h and the organic phase separated, dried (MgSO_4), and concentrated to a yellow oil. Chromatography using pet. ether then 20% ethyl acetate-pet. ether as eluent gave 2,2-dimethyl-1,3-dioxolane-4-methanol-3,5-bistrifluoromethylbenzyl ether as a yellow oil: (CDCl_3) δ 1.4 (3H, s), 1.45 (3H, s),

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3.6-3.65 (2H, m), 3.7-3.8 (1H, m), 4.1-4.15 (1H, m), 4.3-4.4 (1H, m), 4.7 (2H, s), 7.8 (3H, s).

5 b) The product from a) above was dissolved in 150ml THF and allowed to stand for 18h with 30ml 2N hydrochloric acid. THF was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated sodium carbonate solution. The organic phase was separated, dried (MgSO_4) and concentrated to give 1-glycerol-(3,5-bis(trifluorobenzyl)ether as a yellow oil:
10 (CDCl_3) δ 2.0 (1H, s), 2.6 (1H, s), 3.6-3.7 (3H, m), 3.7-3.8 (1H, m), 3.9-4.0 (1H, m), 4.7 (2H, s), 7.8 (2H, s), 7.85 (1H, s).

15 c) A solution of the diol from b) above in 200ml dichloromethane was cooled in an ice-water bath, and treated with a solution of 1.1 equivalents sodium metaperiodate in 100ml water. A further 1g of sodium metaperiodate was added after 3h. The reaction was allowed to stand for 48h, the dichloromethane layer separated, dried (MgSO_4), concentrated *in vacuo* and purified by chromatography using 20% ethyl
20 acetate-pet. ether as eluent, to give [(3,5-bis(trifluoromethylphenyl)methyloxy] ethanol as a clear oil. Bp. 94°C/1.31 mBar.

25 d) To a stirred solution of the aldehyde (3.3mmol) from c) above in 5ml anhydrous diethyl ether under a nitrogen atmosphere was added phenylmagnesium bromide (3.0M solution in diethyl ether, 1.3ml). The reaction was partitioned between ethyl acetate-saturated ammonium chloride after 2h. The organic phase was separated, dried (MgSO_4), concentrated
30 and chromatographed using 20% ethyl acetate-pet. ether as eluent, to give 1-[(3,5-bis(trifluoromethylphenyl)methyloxy]-

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2-hydroxy-2-phenyl ethane as a clear oil. (CDCl_3) δ 3.6-3.8 (2H, m), 4.7 (2H, s), 4.95-5.05 (1H, m), 7.2-7.4 (5H, m), 7.7-7.8 (2H, m).

5 e) A solution of the alcohol (6.9mmol) from d) above in 5ml diethyl ether was treated with triethylamine (1.44ml) followed by methanesulphonyl chloride (0.8ml). The reaction was stirred for 2h then partitioned between ethyl acetate-water. The organic phase was separated, dried (MgSO_4) and concentrated to a
10 yellow oil. Purification by chromatography using 10% ethyl acetate-pet. ether as eluent gave the mesylate as a pale yellow oil.

f) A mixture of the mesylate (0.7mmol) from e) above and
15 1.2 equivalents of the sodium salt of imidazole in 4ml DMF/THF (1:1) was allowed to stand overnight. The reaction was partitioned between diethyl ether-water, the organic phase separated, dried (MgSO_4), concentrated *in vacuo* and purified by chromatography using 20% ethyl acetate-pet. ether as eluent to
20 afford the title compound as a clear oil: (CDCl_3) δ 4.1-4.15 (2H, m), 4.6-4.7 (2H, m), 5.4-5.45 (1H, m), 7.0 (1H, s), 7.1 (1H, s), 7.15-7.2 (2H, m), 7.3-7.4 (3H, m), 7.6-7.65 (3H, m), 7.8 (1H, s).

EXAMPLE 3

25 (±)-1-[(3,5-Bistrifluoromethylphenyl)methoxy]-2-N(2-nitroimidazole-2-phenyl ethane

A suspension of 2-nitroimidazole (2.5mmol) in 3ml anhydrous THF was stirred under nitrogen and treated with sodium hydride (1.1 equivalents of an 80% dispersion in oil).
30 The anion was allowed to form over 2h prior to being reacted in

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an analogous manner described in Example 2 to give the title compound as a yellow oil. (CDCl₃) δ 4.1-4.2 (2H, m), 4.6-4.8 (2H, m), 6.5-6.6 (1H, m), 7.1-7.4 (7H, m), 7.6 (2H, s), 7.8 (1H, s)

5

EXAMPLE 4

(±)-2-N(2-aminoimidazole)-1-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-phenyl ethane

1-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-2-N(2-nitroimidazole)-2-phenyl ethane (Example 3) (60mg) was dissolved in 10ml methanol and was hydrogenolysed over 100mg Pd/C at 50 psi for 3h. The catalyst was removed by filtration, the filtrate concentrated *in vacuo* and purified by chromatography using methanol-ethyl acetate as eluent, to give the title compound as an oil. (CDCl₃) δ 4.0-4.2 (4H, m), 4.6-4.7 (2H, m), 5.3-5.4 (1H, m), 6.6-6.7 (2H, m), 7.2-7.4 (5H, m), 7.7 (2H, s), 7.8 (1H, s).

15

EXAMPLE 5

(±)-1-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-N(4-nitroimidazole)-2-phenyl ethane

20 The title compound was prepared in an analogous manner to that described in Example 3 using 4-nitroimidazole (6.6mmol): (CDCl₃) δ 4.1-4.2 (2H, m), 4.7 (2H, s), 5.2-5.3 (1H, m), 7.2-7.3 (2H, m), 7.4-7.45 (3H, m), 7.55 (1H, s), 7.6 (2H, s), 7.8 (2H, 2).

25

EXAMPLE 6

(±)-1-[(3,5-Bis(trifluoromethyl)phenyl)methoxy]-2-N-morpholino-2-phenyl ethane hydrochloride salt

- 25 -

A solution of 2,5-dihydrofuran (0.11ml) in methanol (10ml) was cooled to -78°C. Ozone gas was bubbled through the solution until a blue colouration developed. The mixture was flushed with nitrogen and then sodium cyanoborohydride (0.22g) was added. After stirring at -78°C for 10 minutes, a solution of 1-[3,5-bistrifluoromethylphenyl)methyloxy-2-amino-2-phenyl ethane in methanol (8ml) was added dropwise and the reaction mixture stirred at 0°C for 3h. The reaction was quenched by addition of acetic acid, and solvent was removed *in vacuo*. 10% Sodium hydroxide solution was added to the residue and the product extracted into dichloromethane (x 3). The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The product was purified by chromatography on silica using 20% → 30% → 40% ethyl acetate in petrol as eluent. The product was dissolved in diethyl ether and a methanolic solution of hydrogen chloride was added. Solvent was removed *in vacuo* and the title compound obtained by trituration with diethyl ether. MS (CI⁺) m/z 434 ((M+1)⁺ 100%).

EXAMPLE 7

(±)-1-[3,5-Bistrifluoromethylphenyl)methyloxy]-2-N-(piperidine-2,6-dione-2-phenyl ethane

A solution of 1-[3,5-bistrifluoromethylphenyl)methyloxy-2-amino-2-phenyl ethane (0.28g) in toluene (5ml) was added to a solution of glutaric anhydride (0.088g) in toluene (10ml) and the reaction mixture heated at reflux for 20h. Solvent was removed *in vacuo* and the crude material purified by chromatography on silica using 15% ethyl acetate in petrol as eluent. The title

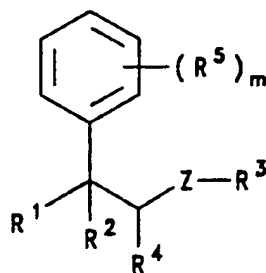
- 26 -

compound was recrystallised from ethyl acetate-petrol. MS (CI⁺)
m/z 460 ((M+1)⁺ 80%).

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Claims

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

15 R^1 represents a nitrogen containing aromatic or non-aromatic heterocycle optionally substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy, oxo, thioxo, halo, trifluoromethyl, nitro, NR^aR^b , NR^aCOR^b , $CONR^aR^b$, CO_2R^a , SO_2R^a and CH_2OR^a , where R^a and R^b each
 20 independently represent H, C_{1-6} alkyl or phenyl optionally substituted by C_{1-6} alkyl, halo or trifluoromethyl;

R^2 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

R^3 represents C_{1-3} alkyl substituted by a phenyl group which may itself optionally be substituted by one
 25 or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^c , SOR^c , SO_2R^c , OR^c , NR^cR^d , NR^cCOR^d , NR^cCOOR^d , $COOR^c$ and $CONR^cR^d$;

R^4 represents H, C_{1-6} alkyl or C_{2-6} alkenyl;

each R^5 independently represents C_{1-6} alkyl,
 30 C_{1-6} alkoxy, halo or trifluoromethyl;

Z represents O or S; and

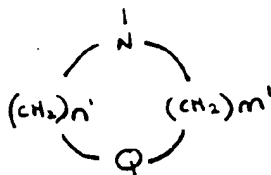
m represents 0, 1, 2 or 3.

2. A compound according to claim 1 wherein R^1 is a 5- or 6- membered heterocycle and may contain, in

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addition to the nitrogen atom, one or more heteroatoms selected from O, S and N, or groups NR^8 , where R^8 is H or C_{1-6} alkyl.

3. A compound according to claim 1 wherein R^1 is a group of the formula



10

wherein Q is CH_2 , NR^8 where R^8 is as hereinbefore defined, O or S, n^1 is 1, 2 or 3 and m^1 is 1 or 2 with the proviso that when Q is NR^8 , O or S neither n^1 nor m^1 is 1; which group can be optionally substituted by one or two oxo groups or C_{1-6} alkyl groups.

15

4. A compound according to claim 1 wherein R^1 is 5 imidazdyl substituted by a nitro or amino group.

5. A compound according to claim 1 herein R^1 is morpholino.

20

6. A compound according to any of claims 1 to 5 wherein R^2 and R^4 are hydrogen or methyl.

7. A compound according to any of claims 1 to 5 wherein R^3 is C_{1-3} alkyl substituted by a phenyl group bearing 1 or 2 substituents on the phenyl ring.

25

8. A compound according to claim 7 wherein R^3 is methyl substituted by 3, 5-disubstituted phenyl.

9. A compound selected from

(+)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(2,5-dimethylpyrrole)-2-phenylethane;

30

1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(imidazole)-2-phenylethane;

(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(2-nitroimidazole)-2-phenylethane;

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(±)-2-N(2-aminoimidazole)-1-[3,5-
(bistrifluoromethylphenyl)methyloxy]-2-phenylethane;
(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]-2-N(4-
nitroimidazole)-2-phenylethane;
5 (±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]2-N-
morpholino-2-phenylethane;
(±)-1-[3,5-(bistrifluoromethylphenyl)methyloxy]2-N-
(piperidine-2,6-clione-2-phenylethane
and salts and prodrugs thereof especially the
10 pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising
one or mono compounds of formula (I) in association with
a pharmaceutically acceptable carrier.

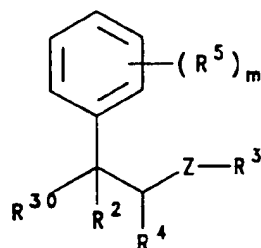
11. The use of a compound according to any of
15 claims 1 to 10 in the preparation of a medicine from the
treatment of a condition caused by an excess of
tachykinin activity.

12. A method of treatment or prevention of
physiological disorder associated with an excess of
20 tachykinin which method comprises administration to a
patient in need thereof of a tachykinin reducing amount
of a compound of formula (I) or a composition comprising
a compound of formula (I) as defined in any of claims 1
to 7.

25 13. A method of preparation of a compound
according to claim 1 which comprises the reaction of a
compound of the formula (II)

30

- 30 -



(II)

- 10 wherein R^2 , R^3 , R^4 , R^5 , Z and m are as defined for
 formula (I) above and R^{30} represents a leaving group, and
 a metalised aromatic heterocycle of formula R^1-M wherein
 R^1 is as defined for formula (I) and M represents a
 metal, such as an alkali metal, for example sodium or
 15 lithium, or with a non-aromatic amine R^1-H , optionally
 in the presence of a tertiary amine base.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/02559

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D207/325; C07D233/91;	A61K31/40; C07D233/88;	C07D233/60; C07D295/084; A61K31/415 A61K31/535
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 499 313 (MERCK SHARP & DOHME LTD) 19 August 1992 see claim 1 ----	1-11,13
A	US,A,2 928 835 (JACOB) 15 March 1960 see column 2, line 23 - line 28 ----	1-9
P,X	WO,A,9 324 465 (MERCK SHARP & DOHME LTD.) 9 December 1993 see claim 1 ----	1-11,13
P,A	EP,A,0 522 808 (MERCK SHARP & DOHME LTD.) 13 January 1993 see claim 1 ----	1-11,13
P,A	EP,A,0 520 555 (MERCK SHARP & DOHME LTD.) 30 December 1992 see claim 1 -----	1-11,13
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
02 MARCH 1994	18. 03. 94	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	GETTINS M.P.	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9302559
SA 83543

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/03/94

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		JP-A- 5186466	27-07-93
